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The temporal characteristics of seizures in neonatal hypoxic ischemic encephalopathy treated with hypothermia

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ABSTRACT

Purpose: The characteristics of electrographic seizures in newborns with hypoxic-ischaemic encephalopathy (HIE) treated with therapeutic hypothermia (TH) are poorly described. This retrospective, observational study provides reference data on the characteristics of seizures and their evolution over time in newborns with HIE receiving whole-body TH.

Method: The cohort under analysis included 23 infants with HIE and seizures defined by multi-channel EEG recordings. Clinical presentation, details of TH and antiepileptic drugs used were recorded. Time from first to last-recorded electrographic seizure (seizure period) was calculated. Temporal characteristics of seizures – total burden, duration, number, burden in minutes per hour, distribution of burden over time (temporal evolution), time from seizure onset to maximum seizure burden (T_{msb}), T_1, and time from T_{msb} to seizure offset, T_2 – were analysed.

Results: The median age at electrographic seizure onset was 13.1 h (IQR: 11.4 to 22.0). T_{msb} was reached at a median age of 19.4 hours (IQR: 12.2 to 29.7). Median seizure period was 16.5 h (IQR: 7.0 to 49.7), median number of seizures per hour was 1.9 (IQR: 1.0 to 3.3). The seizure burden was 4.0 min/h (IQR: 2.0 to 7.0). There was no consistent pattern in the temporal evolution of seizures in neonates treated with TH. The skewness was neither positive nor negative (p-value = 0.15), there was no difference between the duration of T_1 and T_2 (p-value = 0.09) and no difference in the seizure burden between T_1 and T_2 (p = 0.09).

There was an association between T_{msb} and Phenobarbital (PB) administration ($r = 0.76$, p-value < 0.001).

Conclusion: There is no consistent temporal evolution of seizure burden in neonates treated with TH. Seizures are diffuse, and their characteristics are variable.

1. Introduction

The outcome of neonatal encephalopathy secondary to birth asphyxia has been improved by therapeutic hypothermia (TH) [2,3,12]. The precise mechanism through which TH exerts its effect is unclear; however, its role in neuroprotection is probably multifactorial [17,38].

Seizures occur in moderate and severe hypoxic ischemic encephalopathy (HIE) [21,29]. The temporal distribution of these seizures is not uniform, with a short period of high electrographic seizure burden followed by a longer period of low seizure burden, resulting in an accumulation of seizures near the time of seizure onset (a positive skew) [23]. Seizures in human newborns with HIE may exacerbate the initial hypoxic ischemic injury [1,14,25]. Neonatal seizures are difficult to control, and studies performed before the widespread use of TH show that traditional first and second line anti-epileptic drugs (AEDs) are often ineffective [7,40].

There is emerging evidence that TH reduces overall seizure burden and may contribute to improved neurodevelopmental outcome [22,32,33]. The mechanisms through which TH exerts an anti-epileptic effect are unclear. Hypothermia has been shown to suppress the release of glutamate in animal models thus reducing excitotoxicity [8,18]. TH may also enhance the anti-epileptic effect of phenobarbital (PB). There is conflicting evidence regarding changes in pharmacokinetics due to the administration of PB in

Abbreviations: TH, Therapeutic hypothermia; PB, Phenobarbital; HIE, hypoxic-ischaemic encephalopathy; AED, anti-epileptic drug.

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newborns during TH [13,41]; however, effects on the evolution of the background EEG have been observed [37].

The temporal characteristics of electrographic seizures in normothermic infants with HIE have been well described [9,23,31]. Low et al., compared the differences in overall electrographic seizure burden between normothermic and hypothermic infants [22]. There are relatively few studies which investigate in detail the temporal characteristics of electrographic seizure burden in newborns with HIE treated with TH. Studies have described the age of seizure onset in newborns with HIE who receive TH and illustrated that the age of electrographic seizure onset is variable in these infants [15,39]. However, these studies lacked details on the distribution of electrographic seizures over time (temporal evolution), such as number of seizures per hour, seizure burden per hour, and measures of how seizures change over time. Description of these characteristics is important as it adds to the understanding of the impact of TH on seizures in HIE and provides a benchmark against which the efficacy of new anti-seizure treatments can be assessed in the context of emerging new therapies, in the era of 'Therapeutic Hypothermia Plus'.

The aim of this study was to investigate the temporal characteristics of seizures i.e. seizure period (the period between first and last recorded electrographic seizure), number of seizures per hour, seizure burden per hour and the temporal evolution of seizures in newborns with HIE receiving whole-body TH and standard AED therapy.

2. Materials and methods

2.1. Population

Infants with acute HIE treated with TH were enrolled for continuous video EEG monitoring studies in the neonatal intensive care units (NICU) of Cork University Maternity Hospital (CUMH) and University College London Hospitals (UCLH). All EEG research studies are conducted with approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Ireland, and the National Health Service in the UK, via the Integrated Research Application Service. Parental written, informed consent was obtained for all newborns recruited for EEG monitoring studies. Newborns were cooled according to the entry criteria and guidelines set by the UK Total Body Hypothermia for Neonatal Encephalopathy (TOBY) cooling registry [36]. A clinical grade of encephalopathy was assigned to infants using the modified Sarnat score at 24 h of age [21]. Infants with electrographic seizures were included in this retrospective study if they were term (>37 weeks gestation), had HIE (≥ 2 of the following criteria: initial arterial or capillary pH <7.1, Apgar score <6 at 5 min, a continued need for resuscitation after birth, clinical evidence of encephalopathy), had no complicating illness such as meningitis, were treated with TH within 6 h of birth and underwent continuous video EEG monitoring from within 12 h of birth.

2.2. EEG recordings

EEG recording methods were identical in both hospitals. EEG electrodes were applied to the scalp at F3, F4, C3, C4, T3, T4, O1, O2, and CZ (according to the international 10–20 system of electrode placement, as modified for neonates). P3 and P4 electrodes were also applied whenever possible. NicOne EEG monitors (CareFusion NeuroCare, Middleton, Wisconsin, USA) were used to record continuous video-EEG recordings for approximately 96 h. Recordings commenced as soon as possible after birth. Bilateral amplitude integrated EEG (aEEG) traces were displayed simultaneously from the right and left fronto-central regions (F4-C4 and F3-C3) and used by neonatologists as an aid to clinical decision making. The multi-channel EEG recordings were analysed and annotated retrospectively.

2.3. Anti-epileptic drug treatment

First line AED treatment was identical in both centres with infants receiving 20 mg/kg of phenobarbital intravenously (IV) for clinically suspected seizures or seizures detected on aEEG or EEG. Clinicians did not have continuous access to the interpretation of the EEG by the neonatal neurophysiologist which was performed post-hoc. Unresponsive or recurrent seizures were treated with an additional dose of Phenobarbital 10 mg/kg IV. The second line AED in CUMH was phenytoin and midazolam in UCLH. Neonates received regular maintenance doses of AEDs on completion of each loading dose. Levels of AEDs were not measured in all neonates in the cohort.

2.4. Data acquisition and analysis

The medical records of each infant were reviewed. Clinical presentation, duration of TH, types of AED, dose and time of administration were noted. A response to AED was defined as a complete cessation of seizures for at least 12 h after AED administration.

An electrographic seizure was defined as repetitive rhythmic activity of greater than 10 s duration, with a distinct beginning, middle and end [10]. All electrographic seizures were annotated from the start of each seizure on any channel to the end of the seizure on any channel. Seizures were annotated by two experienced neonatal neurophysiologists and agreed by consensus. Inter-observer agreement for seizure detection based on the visual interpretation of multi-channel EEG has been shown to be high [34]. Seizure annotations were converted into a time series, where 1 represented the presence of a seizure and 0 the absence of a seizure. This time series was sampled at 1 Hz. The seizure annotation time series was then cropped between the start of the first recorded EEG seizure and the end of the last recorded EEG seizure. The length of this period was recorded (seizure period). Total seizure burden was defined as the accumulated duration, in minutes, of all seizures recorded in each infant during EEG monitoring [10,23]. To further investigate the temporal evolution of seizure burden, the seizure annotation time series of each newborn was then segmented into two periods; the time between the first recorded seizure and the maximum seizure burden (T_1), and the time between the maximum seizure burden and the last recorded seizure (T_2). The time of maximum seizure burden (T_{msb}) was defined as the mid-point of an hour long window shifted in time by 1s across the full EEG recording that contained the maximum duration of seizure. Within these two periods, the seizure burden per hour, the seizure duration and number of seizures per hour were measured. All measures of the seizure characteristics were based on the annotation of the EEG by the neonatal neurophysiologist.

2.5. Statistical analysis

Continuous data were described using the median, the interquartile range (IQR), minimum and maximum values. The symmetry of the temporal evolution of seizure burden was described using the skewness coefficient. The one-sample Wilcoxon Signed Rank Test (compared to a population median of 0) was used to test if the symmetry was significantly different to that of a uniform distribution (which has a skewness coefficient = 0). A positive skewness coefficient indicates accumulation of seizures near the beginning of the seizure period. Differences between time periods (T_1 and T_2) were tested using the Sign Test, and differences

Table 1
Clinical characteristics of neonates included in the study ($n = 23$) Data are median (interquartile range) or *n*.

Gestational Age (weeks)	40.6 (39.8 to 41.6)
Birth Weight (Kg)	3525 (3190 to 3947)
Gender (M:F)	11:12
Clinical HIE Score	
Moderate: Severe	13:10
5 min Apgar score	4 (2 to 5)
First pH [a]	6.8 (6.7 to 7.0)
Base Excess (mEq/L) [b]	−21.6 (−23.5 to −11.4)

[a] $n = 18$.
[b] $n = 17$.

between moderate and severe HIE subgroups were tested using the Mann-Whitney U test. The strength of the association between two continuous variables was measured using Pearson's correlation coefficient. All statistical analyses were performed using PASW Statistics 18. All tests were two-sided and a p-value <0.05 was considered to be statistically significant.

3. Results

3.1. Patient population

From August 2009 to July 2011, in CUMH and UCL, 43 newborns with moderate or severe HIE were recruited for continuous EEG studies. Both centres used identical criteria for identification of HIE, and the same EEG monitoring techniques. Of the 43 infants with HIE, 23 who received TH developed electrographic EEG seizures and were eligible for inclusion. 15 of these 23 infants were included in a previous study by [22]. 13 infants had moderate HIE (grade 2) and 10 had severe HIE (grade 3). Clinical characteristics are described in Table 1. Four infants had an instrumental delivery (vacuum or forceps), 10 were delivered by emergency caesarean section, and 9 had vertex vaginal deliveries, of whom 3 had shoulder dystocia. All 23 required resuscitation at birth and were eligible for TH under the TOBY criteria. None of the infants developed sepsis, severe electrolyte disturbances or hypoglycaemia during the monitoring period.

Infants received TH for a median of 72.0 h (IQR: 66.8 to 72.0). In four infants cooling was discontinued early. Three of these infants (babies 13, 19, 21 in Fig. 1) had severe HIE and a decision was made to discontinue intensive care. One infant was rewarmed early because of good clinical condition, had a single subsequent three minute electrographic seizure and did not receive AEDs.

EEG monitoring was commenced at between 1.4 and 11.0 h of age at a median age of 5.8 h (IQR: 4.1 to 9.1). EEG monitoring continued for a median of 91.2 h (IQR: 78.0 to 129.0). Infants with moderate HIE were monitored for a median of 87.9 h (IQR: 77.3 to 104.0) and those with severe HIE were monitored for a median of 107.6 h (IQR: 78.0 to 139.6). The duration of monitoring did not differ significantly with grade of HIE (p-value= 0.37). A total of 1581 seizures were recorded in 23 infants. Fig. 1 illustrates the distribution of seizures in infants.

3.2. Electrographic seizure burden

Seizures continued over a median period of 16.5 h from first recorded seizure to last recorded seizure (IQR: 7.0 to 49.7) i.e. the seizure period. The earliest time of seizure onset was 7.0 h and the latest was 81.9 h. The median age at first recorded seizure was 13.1 h (IQR: 11.4 to 22.0). The median age at which maximum electrographic seizure burden (T_{msb}) was reached was 19.4 h (IQR: 12.2 to 29.7). The median seizure burden per hour was 4.0 min/h (IQR: 2.0 to 7.0). In 7 infants, the maximum seizure burden was in excess of 30 min/h. This corresponds to a definition of neonatal status epilepticus [20]. The median age at which the last electrographic seizure was recorded was 37.2 h (IQR: 23.9 to 91.4).

The summary statistics for seizure burden in the 23 infants is shown in Table 2. The skewness coefficient was not significantly different from zero (p-value = 0.15; see Table 2). A positively skewed temporal evolution was seen in infants with severe HIE (median skewness coefficient = 0.68 IQR: 0.31 to 1.39, p-value = 0.03). The median skewness coefficient in infants with moderate HIE was 0.00 (IQR: −0.59 to 0.40, p-value = 0.91). Additional summary statistics for moderate and severe HIE are shown in Table 3.

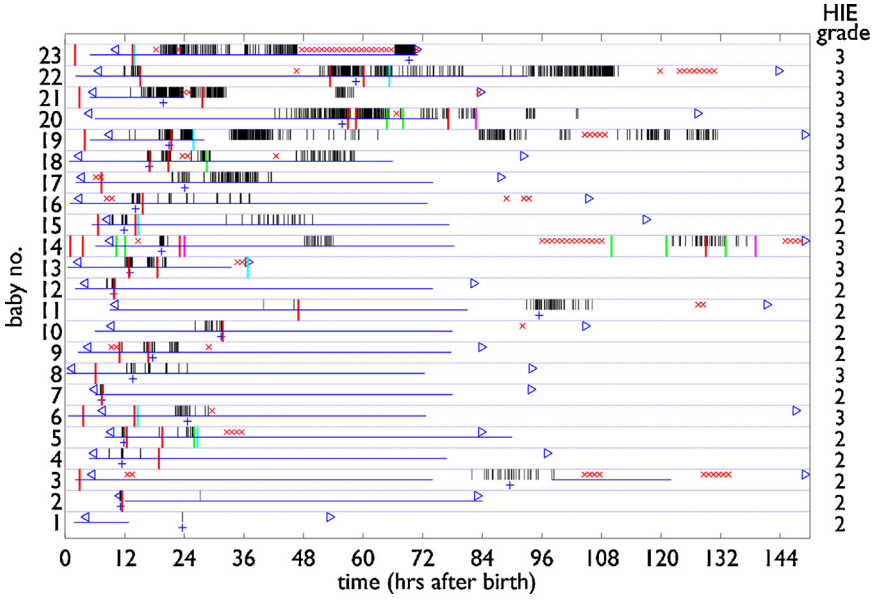

Fig. 1. A graphical representation of the seizure time series combined with clinical information. The start and end of EEG monitoring are denoted by blue triangles. The duration of therapeutic hypothermia is marked by a horizontal blue line. Annotated seizures are denoted by a vertical black line. Missing data are denoted by a red cross. AED administration is denoted by a series of vertical coloured lines: Phenobarbital – red; phenytoin – green; midazolam – cyan; clonazepam – magenta. The maximum seizure burden (peak in seizure burden) is denoted by a blue cross. Infants are ordered in terms of increasing seizure burden.

Table 2
Temporal characteristics of electrographic seizures overall with comparison between T_1 and T_2 ($n = 23$).

	$T_1 + T_2$		T_1		T_2		p-value (from Sign test)
	median	IQR	median	IQR	median	IQR	
Seizure Period (h)	16.5	7.0 to 49.7	2.5	0.5 to 7.4	10.9	3.9 to 38.2	0.09
Total Seizure Burden (min)	55	28 to 190	18	11 to 34	36	13 to 94	0.09
Total Seizure Number	26	13 to 86	9	2 to 14	14	4 to 66	0.007
Missing Data (%)	0	0 to 0.9	0.00	0 to 0	0.00	0 to 0	0.45
Seizure Burden (min/h)	4.0	2.0 to 7.0	9.1	4.4 to 22.8	4.1	1.5to 6.3	0.21
Mean Seizure Duration (s)	125	82 to 238	126	81 to 278	116	69 to 302	0.29
Number of Seizures (per h)	1.9	1.0 to 3.3	2.8	1.7 to 6.4	2.5	0.9 to 3.9	1.00
Skewness[a]	0.35	−0.32 to 0.85	–	–	–	–	0.15[a]

[a] p-value = 0.15 from One-sample Wilcoxon Signed Rank Test
T_1 is the time period between seizure onset and the time of maximum seizure burden
T_2 is the time period between the time of maximum seizure burden and seizure offset
$T_1 + T_2$ is the time period between seizure onset and seizure offset.

Total seizure burden was significantly higher in infants with severe HIE (median 219 min, IQR: 60 to 289) compared with moderate HIE (median 44 min, IQR: 24 to 62, p-value = 0.007). The number of seizures per hour and the seizure burden per hour were not significantly different between moderate and severe HIE. The seizure period and the duration of T_2 were significantly longer in severe HIE (p-value = 0.02 and p-value = 0.03, respectively). The seizure duration was trending towards a lower value in infants with moderate HIE (p-value = 0.051).

3.3. Use of antiepileptic drugs

The use of AEDs was analyzed. AEDs were administered a total 57 times (PB; 38 times) in 22 infants. PB was the first line AED in all cases. AED administration was concurrent with EEG monitoring 49 times (PB; 30 times) in 21 infants. AEDs were administered within the electrographic seizure period 36 times (PB; 24 times) in 16 infants. Of these, 30 administrations were in response to seizures which had an EEG correlate (PB; 22 times). AEDs were administered a total of 11 times (PB; 11 times) in 10 infants during T_1.

PB was given to 10/23 infants prior to the first recorded electrographic seizures due to clinical concerns about seizures. In 7 of these infants PB was administered before EEG monitoring was commenced. The 16/23 infants given PB during the electrographic seizure period received it at a median age of 16.2 h (IQR: 12.6 to 25.4). In 11 of these 16 infants this was the first dose of PB (20 mg/kg). In five infants it was the second dose of PB (10 mg/kg – babies 9, 14, 15, 19 and 21 in Fig. 1). Of these 16 infants, 9 had moderate HIE and 7 had severe HIE.

In the 16 infants who received PB during the electrographic seizure period, the time of PB administration was significantly correlated with T_{msb} ($r = 0.76$, p-value < 0.001). The correlation was influenced by infants with moderate HIE rather than severe HIE (moderate; $r = 0.95$, p-value < 0.001, severe; $r = 0.51$, p-value = 0.25, respectively). The relationship between time of PB administration and T_{msb} is shown in Fig. 2. In 6/9 infants with moderate HIE who received a dose of PB during the seizure period, seizures responded to PB treatment. The response rate was 1/7 in infants with severe HIE (Fisher's exact – p-value = 0.06).

Four infants received phenytoin as a second line AED, at a median age of 27.3 h (IQR: 18.2 to 46.7). Seven infants received midazolam as a second line AED, at a median age of 25.9 h (IQR: 14.7 to 34.3). Two infants received clonazepam as a third line anticonvulsant. The number of infants receiving second line anticonvulsants within the seizure period was too small to estimate the correlation between time of administration and T_{msb}.

4. Discussion

To our knowledge, this is the first quantitative description of the temporal characteristics of electrographic seizures in term newborns with HIE receiving TH, and the evolution of these characteristics over time. It provides further reference data on characteristics of electrographic seizures in HIE during TH: seizure period, number of seizures per hour and seizure burden in minutes per hour. It also provides data on the temporal evolution of these characteristics i.e. distribution of seizure burden over time, time from seizure onset to maximum seizure burden and time from

Table 3
Subgroup analysis of the temporal characteristics of electrographic seizures overall with comparison between T_1 and T_2.

	$T_1 + T_2$		T_1		T_2		p-value (from Sign test)
	Median	IQR	Median	IQR	Median	IQR	
Moderate ($n = 13$)							
Seizure period(h)	14.6	4.6 to 21.0	2.5	0.4 to 5.5	8.8	0.3 to 16.4	1.00
Seizure burden (min/h)	3.9	1.6 to 14.2	9.1	3.5 to 32.3	4.1	1.3 to 41.2	1.00
Seizure duration (s)	176	91 to 302	203	97 to 760	126	81 to 455	0.39
Seizure frequency (seizures/h)	1.2	0.7 to 2.5	2.1	1.3 to 6.8	2.3	0.7 to 4.5	0.58
Skewness	0.00	−0.59 to 0.40					0.91 [a]
Severe ($n = 10$)							
Seizure period (h)	48.1	12.2 to 99.5	4.6	1.1 to 13.6	39.8	7.3to 52.8	0.02
Seizure burden (min/h)	4.1	3.2 to 6.6	9.2	8.4 to 12.9	3.9	1.9 to 6.1	0.11
Seizure duration (s)	87	79 to 142	92	78 to 129	86	60 to 151	0.75
Seizure frequency (seizures/h)	2.9	1.4 to 3.7	4.7	2.3 to 6.3	2.7	1.2 to 3.7	0.34
Skewness	0.68	0.31 to 1.39					0.03[a]

[a] p-value from One-sample Wilcoxon Signed Ranks Test.
T_1 is the time period between seizure onset and the time of maximum seizure burden.
T_2 is the time period between the time of maximum seizure burden and seizure offset.
$T_1 + T_2$ is the time period between seizure onset and seizure offset.

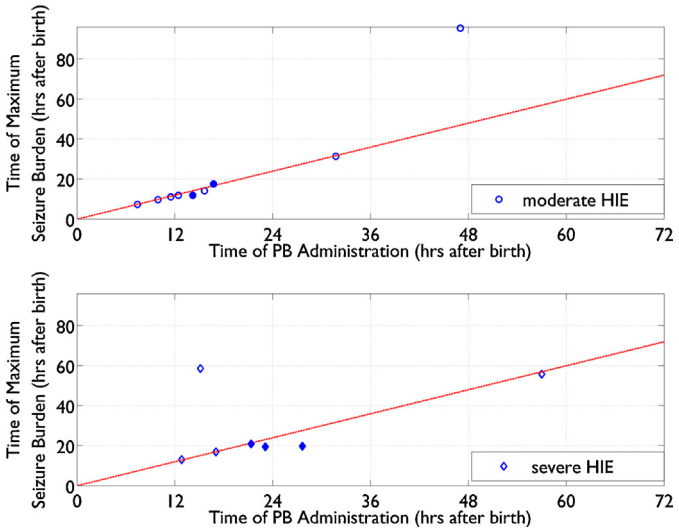

Fig. 2. The relationship between the time of PB administration and the time of maximum electrographic seizure burden across 16 infants with moderate and severe HIE who received PB during the seizure period. The administration of PB is highly correlated with T_{msb} suggesting that either clinical recognition of seizures was associated with PB administration time or that PB administration was interfering with any potential increase in seizure burden. This was the first dose of PB (20 mg/kg) in 11 infants (unfilled markers). It was the second dose (10 mg/kg) in 5 infants (filled markers).

maximum seizure burden to seizure offset. Finally details on the seizure characteristics of infants with moderate and severe HIE are reported separately.

Our previous study demonstrated significantly reduced total seizure burden, and a trend towards lower mean seizure duration, total seizure number and incidence of status epilepticus in newborns with HIE receiving TH compared with normothermic infants with HIE [22]. Our additional assessment of seizure characteristics in an expanded cohort of 23 hypothermic infants strengthens the evidence that hypothermic infants have a lower seizure burden with a more temporally diffuse distribution of seizures (a lower seizure burden per hour) than normothermic infants.

As with our previous study [23], we focussed on the temporal as opposed to the spatial characteristics of EEG seizures. Including a spatial component in the analysis of seizure burden may lead to an improved understanding of the effect of neuroprotective therapies on seizure propagation within the neonatal brain. Future work with a greater number of electrodes will enhance the analysis of seizure burden [27].

The median seizure period in this cohort of infants was 16.2 h. The median seizure period in the normothermic cohort we previously described was 36.6 h [23]. Animal studies have also shown shorter electrographic seizure duration and seizure period in those receiving TH [35]. Electrographic seizure onset in this cohort of infants receiving TH was at a median age of 13.1 h. The latest age at electrographic seizure onset was 81.9 h. While only one neonate appeared to have seizure onset during the period of rewarming, we noticed several instances of seizure reoccurrence during this period suggesting that the increase in metabolism apparent at this time may trigger additional seizures [19]. This wide range of age at seizure onset is comparable to existing studies and coupled with more diffuse temporal distribution of seizures means that detection of neonatal seizures in the context of TH may prove difficult in the absence of continuous long term EEG monitoring [15,39].

In our cohort of neonates treated with TH, the duration of T_1 does not differ from that of T_2, nor does the seizure burden in the two time periods differ significantly. This is in contrast to findings in normothermic neonates where T_2 was significantly longer than T_1 and short term assessment of seizure burden was significantly higher in T_1 compared to T_2 [23]. In fact, the relationship between the seizure burden in T_1 and T_2, while not significant, was the converse of that see in normothermic neonates. As the definitions of T_1 and T_2 are dependent on the definition of T_{msb}, we hypothesize that T_{msb} is occurring closer to seizure onset in newborns treated with TH. This shift in T_{msb} may be altering the skew of the distribution of seizures over time (the temporal evolution) in a significant number of neonates and may result in a shortened overall seizure period. Preliminary analysis of PB administration suggests that it may be PB that is altering T_{msb} as T_{msb} is highly correlated with PB administration time, a finding that was not as apparent in our study of normothermic neonates [23]. This suggests that our observations are not of the temporal evolution of seizures in neonates treated with TH but rather the temporal evolution of seizures in neonates treated with TH and AEDs.

This alteration in T_{msb} may be due to a number of factors. Firstly, the introduction of TH has had the added benefit of more uniform treatment and monitoring of infants with HIE [2]. Secondly, improvements in early EEG or aEEG monitoring of newborns with HIE resulting from the necessity to commence TH within six hours of birth may result in better timing of PB administration. The administration of PB appears to be given earlier in our cohort of neonates treated with TH compared to our cohort of normothermic neonates [23], although differences have not been statistically analysed. Timing of PB administration has been shown, in animal studies, to be an important factor in the efficacy of PB, with early administration proving more effective than administration once seizures are well established [4,11,26]. Finally, TH alters the way PB effects the evolution of background EEG [37], and it is possible that its efficacy is enhanced in the altered milieu of TH.

The role of PB in seizure reduction in the TH cohort is largely confined to infants with moderate HIE. The correlation between T_{msb} and time of PB administration reaches overall significance because of the correlation in the moderate subgroup ($r = 0.95$, p-value < 0.001). Low et al. identified the most significant reduction in seizure burden during TH amongst infants with moderate HIE. In this expanded cohort of 23 infants total seizure burden is significantly higher in those with severe HIE compared with moderate HIE (p-value = 0.007). The overall benefits of TH have been found to be greater in infants with moderate HIE ([2,12,42]). A response rate to PB in hypothermic infants similar to that observed in our study has been reported by [15] with 30% of infants with moderate/severe injury responding to a single dose of PB compared with 100% of those with minimal/no injury evident on MRI.

This study was retrospective and observational and describes the temporal characteristics and temporal evolution of electrographic seizures in infants receiving TH. For this reason, the principle reference time point in this study was the time of electrographic seizure onset, which was reliably recorded due to the early application of continuous EEG monitoring. Future prospective work using continuous EEG, in addition to the use of MRI and investigating perinatal events, may help to establish a relationship between the nature and timing of brain injury and the temporal evolution of neonatal seizures [5,30].

Not all infants in this cohort received TH for a full 72 h. Three infants with severe HIE and one with moderate HIE had TH withdrawn. However, we have included them in this cohort as their exclusion would have led to an over-representation of infants with moderate HIE.

Further work is required to investigate the response to conventional and novel forms of AED treatment in HIE in the context of therapeutic hypothermia. Only larger studies across

several centres with greater numbers of babies will have the ability to characterise the response to PB in infants with HIE [28].

5. Conclusions

The aim of this study was to describe the temporal characteristics and evolution of electrographic seizures in infants with HIE who received TH. Our results contribute new information regarding seizure period, number of seizures per hour and seizure burden per hour in these infants. This cohort differed from the normorthermic cohort we previously described in that we did not identify a consistent positively skewed temporal evolution across the entire group [23]. We found a significant correlation between T_{msb} and PB administration suggesting that we were not describing the temporal evolution of seizure in neonates treated with TH but rather neonates treated with TH and AEDs.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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